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English Summary

Living systems differ from the dead by the ability to sustain themselves actively when subject to altered environmental conditions: they respond and adapt so as to enhance their fitness in the new condition. If the altered condition is a challenge of short duration (a spike) then such adaptation would seem useless if not counter effective, as it displaces the system from its possibly optimal state. Challenges may repeat themselves however, and some living systems are able to adapt in anticipation of second such a challenge. The term "preconditioning" has become widely used to describe this type of vital functions that sustain living systems: this type of function has the system adapt to an initial stimulus in a way that results in an altered response to a subsequent, often stronger stimulus. This thesis analyzes the correlation between the responses to two consecutive transient stimuli, similar in type but increasing in strength, where the second stimulus could be life threatening or inductive of an irreversible pathology. This thesis expands and elaborates upon the definition of this preconditioning. It distinguishes between two types of preconditioning, i.e. progressive preconditioning (PROP) and regressive preconditioning (REP). PROP refers to cases where an initial, non-lethal stimulus makes cells, tissues or whole organisms tolerant to a future, otherwise lethal stimulus. Examples are found in ischemic preconditioning (Murry et al. 1986) and in vaccination (Dirnagl et al. 2003; Iliodromitis et al. 2007; Lin et al. 2014; Michael Bell 2002). REP refers to conditions where an initial small stimulus leads to a disastrous or even fatal response to a second, bigger or similar stimulus, which if given by itself would not have been lethal or pathological. Here allergy and apoptosis progression constitute good examples (Costa et al. 2013; Drouhet et al. 1981; Samarasinghe et al. 2014).

Preconditioning requires networking between multiple components. Accordingly, the present study used systems-biology approaches to discover network principles underlying these two types of adaptation. We first launched a mathematical relationship between the two that can highlight the difference between PROP and REP behavior. Within these mathematical definitions, we introduced novel terms, such as lethality threshold, lethality probability, preconditioning-response and preconditioning coefficient. We, then, defined the emergence of PROP and REP using the three main mathematical criteria that are based on these terms. According to these criteria PROP exists when *(i)* a preconditioning coefficient α_p is smaller than one, and *(ii)* a preconditioning-response coefficient (α_R) is between one and zero, and *(iii)* this for an increasing intensity of two subsequent stimuli ($S_1 \geq S_2$), with the initial stimulus being lower than the lethality (pathology) threshold ($S_1 < T$). REP requires the meeting of the following criteria: *(i)* a preconditioning coefficient α_p greater than one, *(ii)* a preconditioning-response coefficient (α_R) greater than one *(iii)* and this for a decreasing intensity of two stress stimuli ($S_1 \geq S_2$), with the initial stimulus being lower than the lethality threshold ($S_1 < T$).

The next step in our examination of preconditioning was to test whether preconditioning meeting these criteria should be expected to occur in a variety of biological systems. We examined this for the nuclear hormone receptor (NR) network (Chapters 2 and 3) and for the mitoptosis-apoptosis network (Chapter 4). The expectation was addressed by inspecting realistic network models of these two systems.

Nuclear hormone receptors play an essential role in the regulation of the transcription of a great many genes, via their interaction with hormones. We developed a relatively simple mathematical model for a network around two of the nuclear hormone receptors, i.e. the glucocorticoid receptor (GR) and the pregnane-X-receptor (PXR). It involved their two of their target genes, i.e. TAT and CYP3A4, and a common ligand for both, i.e. cortisol (Kolodkin et al. 2013a). We have set up several *in silico* experiments in order to *(i)* examine pharmacokinetic and pharmacodynamic responses in chronic stress situations, *(ii)* identify preconditioning phenomena in diverse conditions, e.g. with respect to various cortisol challenges, (iii) and identify some of the mechanisms that could be in operation. Via simulations, we demonstrated that regulatory signals between these two nuclear receptors could help optimize the body's response to stress episodes. Additionally, we predicted that the activation of PXR by multiple, low-affinity endobiotic ligands is necessary for the PXR-mediated transcriptional response following stress episodes to be significant. This response depended on the presence of basal stress levels and on the nature of the stress episodes themselves. The magnitude of stress inductions was less important when the basal stress levels were high. When the basal stress levels were low, both the magnitude and the delay between the stress episodes were predicted to be factors determining the risk of disease from chronic stress. Similarly, the basal stress levels were determining factors in producing a 'biological memory' that can lessen the response to subsequent stress episodes: progressive preconditioning (PROP). When the basal stress levels were high, the preconditioning influence on the response to the subsequent stress episode was small. However, under certain biological conditions (i.e. reduced intensity of the initial stress episode, reduced delays between stress episodes), a negative biological memory can be generated, increasing the response to subsequent stress episodes and morbidity: regressive preconditioning (REP; see above). Together, we emphasize that for determining the emergent biological response, the way stress episodes are presented is as important as the magnitude of the stress episode. (Chapter 2).

We next expanded the simple nuclear hormone receptor dynamic model (Kolodkin et al. 2013a) described above with both the circadian rhythm of cortisol (Leloup and Goldbeter 2003) and the liver metabolic map (Gille et al. 2010; Thiele et al. 2013). This combination of two kinetic models and a kinetics-naïve metabolic map was simulated using a Quasi steady state Petri net (QSSPN) algorithm (Fisher et al. 2013). For this integral model, we demonstrated that an increase in plasma glucose resulted from either high-frequency

acute stress episodes or from chronic circadian de-synchrony. The combination of these two effects further intensified the glucose production flux from the liver. These predicted increases in glucose production were in line with the variation between people at the pre-diabetic/diabetic borderline as well as between people experiencing less versus more of intensive stress, pregnant women in their last stage of parturition constituting an example of the latter case (Risberg et al. 2016). PROP and REP were observed in silico under certain conditions. Basal internal conditions and magnitude of the stress episodes were determining factors for emergence of either PROP or REP, revealing the large impact of these two temporary features on the type of response: positive or negative with respect to survival (Chapter 3).

Finally, we have constructed a mathematical model based on the molecular evidence available in the literature in order to (*i*) help identify a new, paradoxical role of mitochondria in apoptosis and (*ii*) examine the emergence of PROP and/or REP behavior in apoptosis. Our initial proposal was that mitochondrial dysfunction and autophagy can constitute a strategic form of mitochondrial death, i.e. one that would prevent rather than induce apoptosis. We hypothesized that the intensity and history of mitochondrial autophagy determine whether the outcome is cell survival or apoptosis, although both "mitoptosis" (the former of the two) and "mitochondrial apoptosis" (the latter) use the same mechanism of mitochondrial autophagy. Our simulation results showed that the cell may indeed have a memory of previous ROS damage, which can act through mitochondrial autophagy, causing a limitation of the cell`s response to a subsequent, deadlier ROS exposure. This exemplifies PROP behavior, works pro-survival by reducing apoptosis, and hence corresponds to mitoptosis. When the ROS exposures were too frequent, mitoptosis could not protect the cell from apoptosis and the mitochondrial autophagy promoted rather than blocked the apoptotic route, exemplifying REP (Chapter 4).

In summary, this thesis discusses mechanisms and conditions governing the emergence of preconditioning, by using mathematical modeling techniques. Via the expanded description of preconditioning, we were able to describe the principles, process, conditions and limitations of preconditioning using various complex molecular networks. These examples may help us to identify potential role(s) of preconditioning also in the context of diseases such as metabolic disorder, depression, and cancer. For instance, cancer studies might be accelerated by taking the necrosis-apoptosis-mitoptosis relation and the role of preconditioning in mediating them, into account. The scope and potential applications of the principles we found to rule preconditioning, should be useful for implementation in systems medicine.